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## LET-weighted doses effectively reduce biological variability in proton radiotherapy planning

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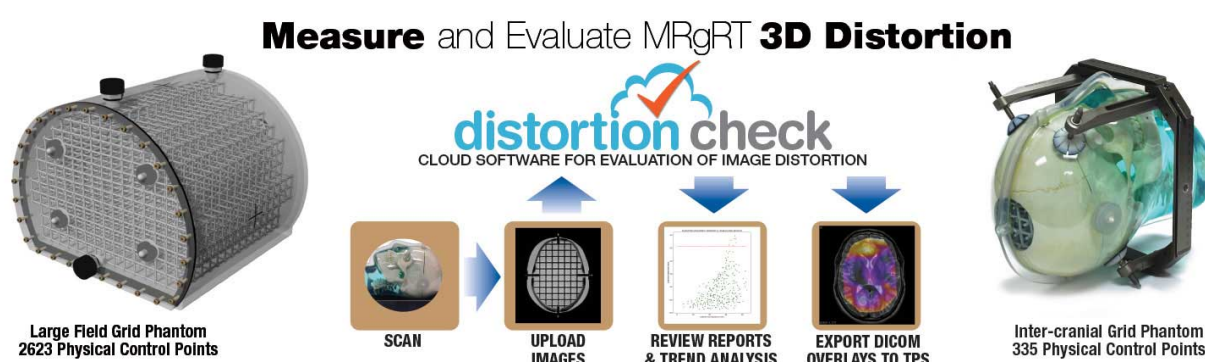
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## PAPER

LET-weighted doses effectively reduce biological variability  
in proton radiotherapy planningStephen J McMahon<sup>1,3</sup> , Harald Paganetti<sup>2</sup> and Kevin M Prise<sup>1</sup><sup>1</sup> Centre for Cancer Research and Cell Biology, Queen's University Belfast, Belfast, United Kingdom<sup>2</sup> Department of Radiation Oncology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, United States of America<sup>3</sup> Author to whom any correspondence should be addressed. Centre for Cancer Research & Cell Biology, Queen's University, Belfast, 97 Lisburn Road, Belfast BT9 7AE, United KingdomE-mail: [Stephen.mcmahon@qub.ac.uk](mailto:Stephen.mcmahon@qub.ac.uk)**Keywords:** proton therapy, linear energy transfer, relative biological effectiveness (RBE)Supplementary material for this article is available [online](#)

## Abstract

Variations in proton relative biological effectiveness (RBE) with linear energy transfer (LET) remain one of the largest sources of uncertainty in proton radiotherapy. This work seeks to identify metrics which can be applied to mitigate these effects in treatment optimisation, and quantify their effectiveness. Three different metrics—dose, dose  $\times$  LET and an LET-weighted dose defined as Dose  $\times (1 + \kappa \text{LET}_D)$  where  $\text{LET}_D$  is the dose-averaged LET—were compared with *in vitro* experimental studies of proton RBE and clinical treatment plans incorporating RBE models. In each system the biological effects of protons were plotted against these metrics to quantify the degree of variation introduced by unaccounted-for RBE uncertainties. As expected, the LET-dependence of RBE introduces significant variability in the biological effects of protons when plotted against dose alone. Plotting biological effects against dose  $\times$  LET significantly over-estimated the impact of LET on cell survival, and typically produced even larger spreads in biological effect. LET-weighted dose was shown to have superior correlation to biological effect in both experimental data and clinical plans. For prostate and medulloblastoma treatment plans, the average RBE-associated variability in biological effect is  $\pm 5\%$  of the prescribed dose, but is reduced to less than 1% using LET-weighting. While not a replacement for full RBE models, simplified metrics such as this LET-weighted dose can be used to account for the majority of variability which arises from the LET-dependence of RBE with reduced need for biological parameterisation. These metrics may be used to identify regions in normal tissues which may see unexpectedly high effects due to end-of-range elevations of RBE, or as part of a more general tool for biological optimisation in proton therapy.

## Introduction

Proton radiotherapy offers significant dosimetric advantages over conventional photon-based therapy, as protons' continuous energy loss gives them a well-defined range with greatest energy deposition at the end of their path. As a result, normal tissues can be spared, reducing side-effects or allowing an escalation of target doses (Newhauser and Zhang 2015).

However, the use of protons is not problem-free. Protons bring new challenges in dosimetry and planning, as variations in particle range with tissue composition can lead to classes of uncertainty not seen in photon radiotherapy (Paganetti 2012, Mohan *et al* 2017). But perhaps more importantly, there are also differences in biological effectiveness between photons and protons which are not typically incorporated in clinical planning.

When different particles are used to deliver the same dose of ionising radiation, differences in biological effects are observed, typically defined in terms of a relative biological effectiveness (RBE)—the ratio between the dose needed to produce a particular biological response with a reference radiation and the dose of a test radiation

which produces the same effect. For protons, a constant RBE of 1.1 relative to photons is typically assumed, and plans are optimised based on physical dose alone (Paganetti 2014).

While this reflects that protons are more biologically effective than photons, it assumes that this effect is a constant independent of dose, tissue type and LET, despite extensive preclinical evidence that proton RBEs are variable (Paganetti 2014). This reflects a significant limitation in proton treatment planning. By considering only the dose delivered, considerable uncertainty is introduced into the biological effect in each voxel due to variations in RBE, schematically illustrated in figure 1(a). While the introduction of a constant RBE factor can account for systematic changes in the average effect (figure 1(b)), large variability can still exist on the level of individual voxels.

The resulting uncertainties in biological effect are often larger than goals for physical uncertainty in treatment plans. As a result, proton therapy is not delivering on its full potential. Incorporation of the LET-dependence of proton RBE could reduce treatment uncertainties and potentially identify RBE ‘hotspots’ which may drive unexpectedly large responses, particularly at the end-of-range which typically occurs in normal tissue (Carabe *et al* 2012).

Empirical analytic proton RBE models have been developed to better understand and quantify these effects. Typically, these models begin from the linear-quadratic cell survival model, and adjust the  $\alpha$  and  $\beta$  parameters with the introduction of LET-dependent terms (Carabe-Fernandez *et al* 2007, Wedenberg *et al* 2013, McNamara *et al* 2015, Jones *et al* 2018). While accurate quantification of RBE would offer the ideal method to account for these effects, these models have seen limited translation to the clinic. In part, this is because these models depend on both the  $\alpha/\beta$  ratio of the target tissue as well as a number of model-specific fitting parameters which carry uncertainties and possible inter-patient variability, which translates into potentially large uncertainties in predicted RBE (Bentzen *et al* 1988, Webb and Nahum 1993, Paganetti 2017).

However, for the purposes of treatment optimisation, full RBE models may not be required to mitigate these effects. It is important to note that even in photon-based therapy, treatments are planned based on physical dose rather than biological effect, and there is considerable systematic uncertainty in the relationship between a given dose and the resulting level of biological effect—as a result of both inter-tissue and inter-patient variations in sensitivity (West *et al* 1993, Scheenstra *et al* 2014, Alsbeih *et al* 2016). Despite this, dose-based planning is effective in photon therapy because no variation in biological response is expected between voxels in the same tissue exposed to different doses. Thus, by assuming tissue dose responses are monotonic—biological effects smoothly and continuously increase with dose—treatment plans can be efficiently optimised, even if the exact magnitude or functional dependence on dose is not known.

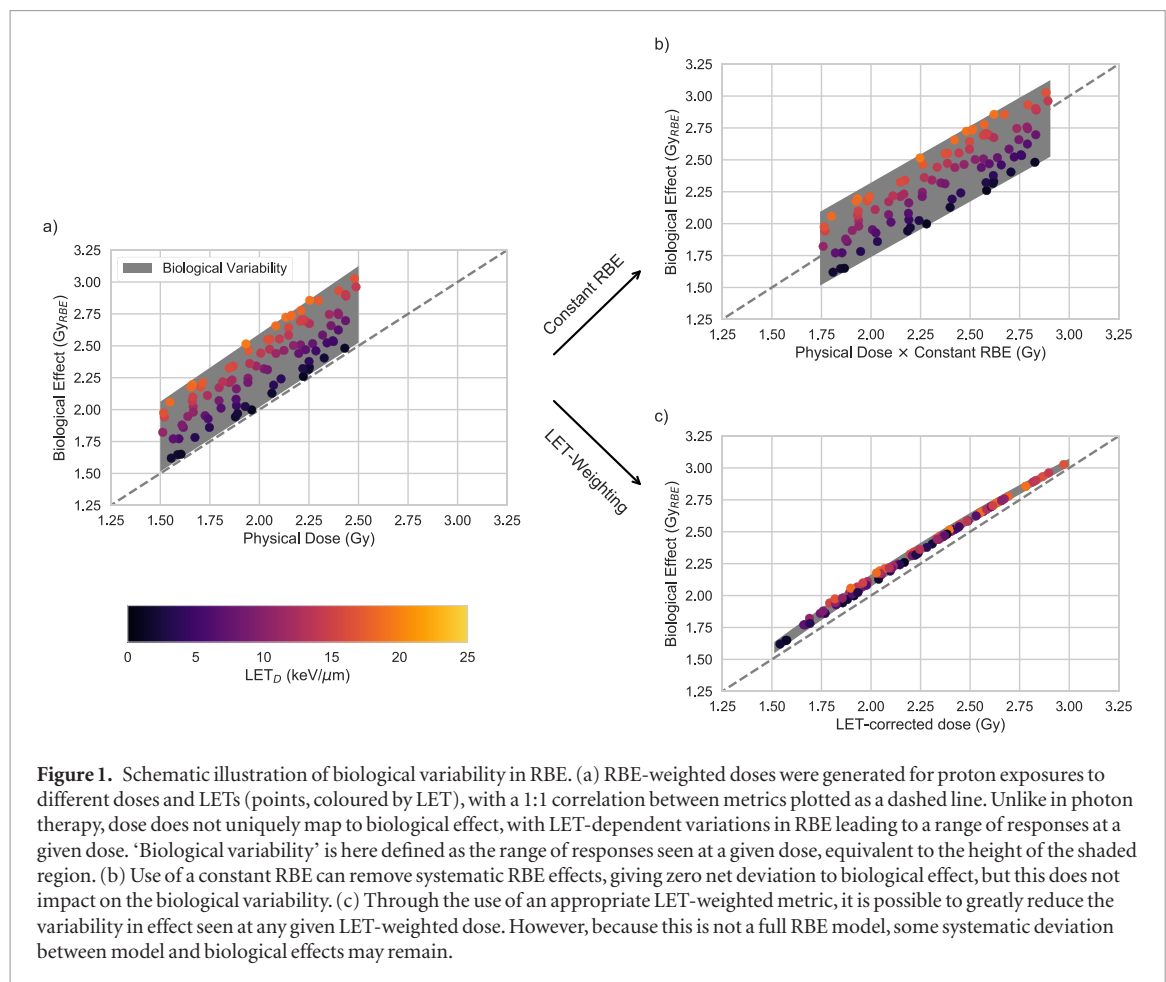
A similar concept can be applied to proton therapy—even if there remains significant systematic uncertainties in RBE, metrics which combine physical parameters in a way which better correlates with response have the potential to serve as useful tools for treatment optimisation. The potential for this approach is highlighted by the observation that most commonly used RBE models are highly correlated in their predictions of RBE-weighted dose, suggesting a simpler metric which captures key aspects of the LET-RBE dependence may be able to provide most of the benefit of full RBE models for optimisation. This is conceptually illustrated in figure 1(c), showing an illustration of a metric which is nearly monotonically related with biological effect, substantially reducing biological variability at any given point even if it does not fully account for systematic differences in RBE.

In this vein, groups have proposed optimisations based on the physical quantities of dose and LET as a proxy for response, rather than RBE models (Bassler *et al* 2010, Giantsoudi *et al* 2013, Unkelbach *et al* 2016, Wan Chan Tseung *et al* 2016). However, it remains unclear what metric is best suited to this purpose, or how effectively these simple metrics reduce biological variability in treatment planning. In this work, we evaluate dose, dose  $\times$  LET and a weighted average of these quantities to evaluate their performance in reducing RBE-related variability as an alternative to ‘true’ RBE models.

## Methods

### Biological variability

Considering dose alone is insufficient to predict the response of cells exposed to proton irradiation, due to the LET-RBE relationship. In this work, we use the term ‘biological variability’ to describe the range of responses seen for a given dose. This can be quantified in terms of survival (as in figure 2) or photon-equivalent RBE-weighted dose (figures 4 and 6). For example, for the points illustrated in figure 1, it can be seen that points exposed to a dose of 2 Gy can see effects equivalent to doses ranging from approximately 2 Gy to 2.6 Gy of photons, or a variability of  $\pm 0.3$  Gy. It is important to note that this variability remains even when the average error in effect is corrected to zero via a constant RBE (as in figure 1(b)), and can be reduced to effectively zero even when systematic uncertainty in the absolute value of RBE remains (as in figure 1(c)).



To quantify biological variability as in the clinical plans below, the variability at each dose was calculated as the size of the 95% confidence interval of biological responses seen at that dose in a given tissue. This was then averaged across the whole dose range to provide average uncertainties for different approaches.

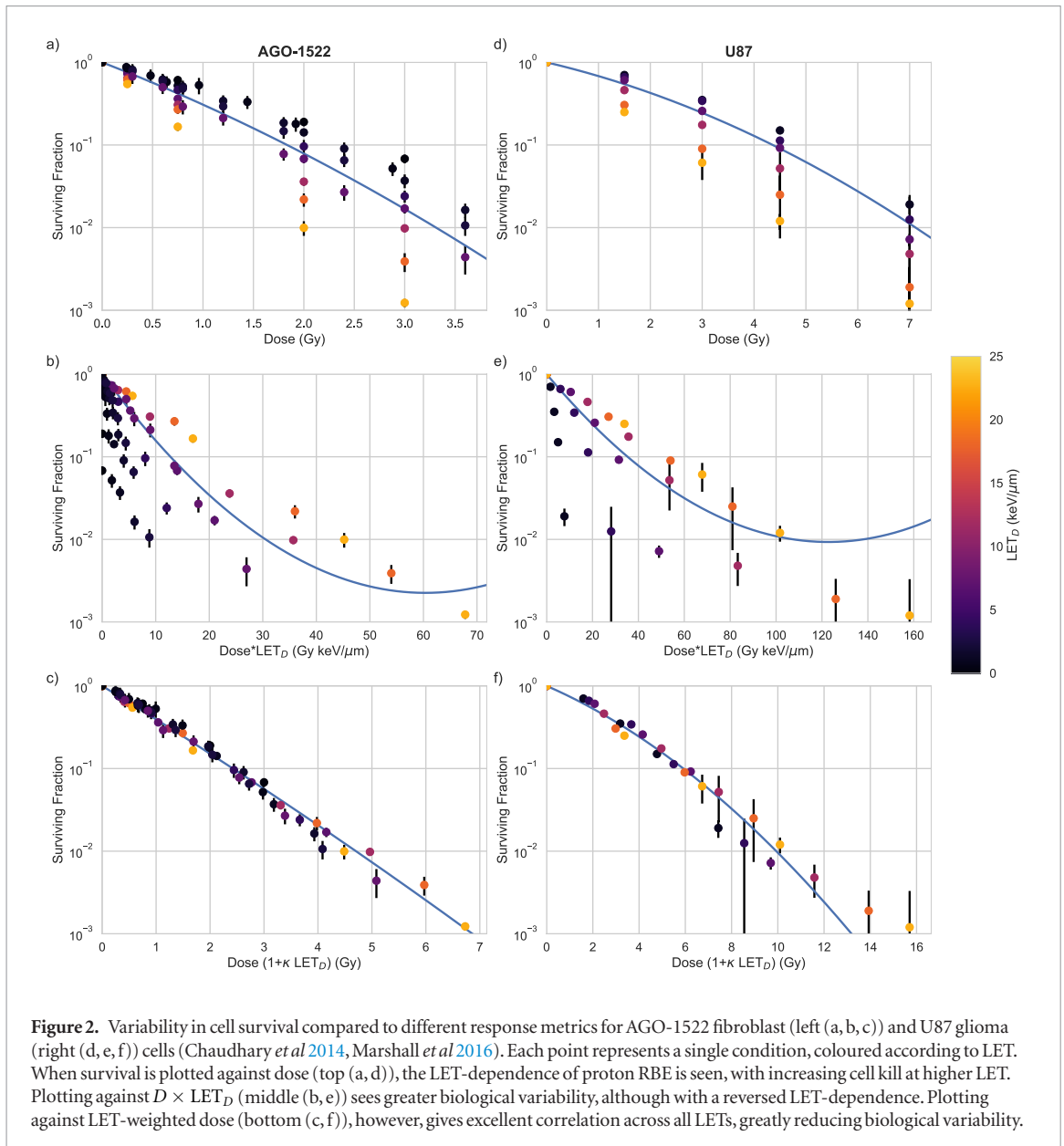
### Radiation response metrics

Three response metrics have been studied: physical dose,  $D$ ; dose-LET product,  $D \times \text{LET}_D$  (suggested by some authors as an RBE surrogate); and a weighted average of these metrics. This weighted average is given by  $D + \kappa D \times \text{LET}_D = D \times (1 + \kappa \text{LET}_D)$ , where  $\kappa$  is an empirical fitting parameter with units of  $\mu\text{m keV}^{-1}$ . This approach can potentially be applied to either track- or dose-averaged LET. Track-average LET ( $\text{LET}_t$ ) represents the simple arithmetic mean of the LETs of each individual particle in a field. However, this neglects the fact that a high-LET particle deposit proportionally more dose than a low-LET particle, which may lead to high-LET particles having a greater contribution to observed biological effect. To address this, the dose-averaged LET ( $\text{LET}_D$ ) weights each particle's LET by the dose it deposits in the target volume, and is chosen as the metric in this work (Guan *et al* 2015).

As it is well established that the primary effect of radiation is an increase in the  $\alpha$  term of the LQ response curve, the LET-weighted dose metric is conceptually similar to the behaviour of  $\alpha$  in a number of RBE models, giving similar low-dose, low-LET trends (Carabe-Fernandez *et al* 2007, Wedenberg *et al* 2013, McNamara *et al* 2015). However, it includes only one parameter and deliberately does not attempt to convert to a tissue-specific biological effect or photon-equivalent dose, thus avoiding dependence on specific tissue biological parameters which are frequently poorly known.

### Cell survival data

Survival data for cells exposed to protons was obtained for AGO-1522 fibroblasts and U87 glioma cells from the literature (Chaudhary *et al* 2014, Marshall *et al* 2016). Clonogenic cell survival was measured at various positions across either pristine or spread out Bragg peaks (SOBPs) to quantify the dose response curves at different energies, with doses from 0 to 7 Gy and  $\text{LET}_D$  from 1 to 25  $\text{keV } \mu\text{m}^{-1}$ . For each position,  $\text{LET}_D$  was calculated using Monte Carlo simulations of the beamline using Geant4 (Agostinelli *et al* 2003). Further details on experimental design can be found in the original papers (Chaudhary *et al* 2014, Marshall *et al* 2016). Although these studies used SOBPs generated in different fashions (passive scattering and pencil beam scanning, respectively), comparison



of AGO-1522 dose responses from both papers found no significant difference in response at similar LETs, so these data were pooled and analysed as a single dataset.

Survival from these experiments was plotted against each of the three candidate metrics. Correlation between each metric and biological response was assessed by fitting a function of the form  $\ln(S) = -AM - BM^2$ , where  $M$  is one of the three metrics, and  $A$  and  $B$  are fitting parameters.

For  $M = D$ , this reduces to the standard linear-quadratic dose response model with  $A$  and  $B$  taking units of  $\text{Gy}^{-1}$  and  $\text{Gy}^{-2}$ . These units are also used for LET-weighted dose. For the  $M = D \times \text{LET}_D$  case,  $A$  and  $B$  take units of  $\mu\text{m keV}^{-1} \text{Gy}^{-1}$  and  $\mu\text{m}^2 \text{keV}^{-2} \text{Gy}^{-2}$ , respectively. While the dose-LET product can be rescaled to units of Gy by multiplying by a  $\kappa$ -like term, this does not impact on the overall correlation.

### Spread out Bragg peak RBE comparison

Experimental data necessarily covers only a limited range of combinations of dose and  $\text{LET}_D$ . To evaluate the metrics at a wider range of conditions and to better understand their underlying behaviour in this experimental dataset, RBE was modelled analytically across the whole SOBP. Dose and  $\text{LET}_D$  distributions were calculated for a 2 Gy SOBP delivered with 62 MeV protons with 10 mm range modulation by passive scattering, corresponding to that used experimentally (Chaudhary *et al* 2014).

At each point along the SOBP, RBE-weighted doses were calculated based on experimentally-determined parameters. In this case, the explicit empirical RBE model used by Chaudhary *et al* in these publications was applied, which gave survival as:



$$S = e^{-(\alpha_x + \lambda \text{LET}_D)D - \beta_x D^2}.$$

Where  $\alpha_x$  and  $\beta_x$  are the experimentally-determined x-ray radiosensitivity parameters, and  $\lambda$  is an empirical fitting parameter describing the LET-dependence of  $\alpha$  for protons (Chaudhary *et al* 2014, Marshall *et al* 2016). For these experiments, these parameters were determined to be:  $\alpha = 0.77 \pm 0.02 \text{ Gy}^{-1}$ ,  $\beta = 0.06 \pm 0.01 \text{ Gy}^{-2}$  and  $\lambda = 0.06 \pm 0.01 \text{ Gy}^{-1} \mu\text{m keV}^{-1}$  for AGO-1522 cells; and  $\alpha = 0.13 \pm 0.02 \text{ Gy}^{-1}$ ,  $\beta = 0.05 \pm 0.02 \text{ Gy}^{-2}$  and  $\lambda = 0.026 \pm 0.003 \text{ Gy}^{-1} \mu\text{m keV}^{-1}$  for U87 cells. These RBE-weighted doses were then plotted against each of the three metrics.

### Clinical treatment plan comparison

Finally, two clinical treatment plans were evaluated: one medulloblastoma and one prostate. Clinically delivered treatment plans were re-simulated using TOPAS (Perl *et al* 2012), as described elsewhere (McNamara *et al* 2015), to provide dose and  $\text{LET}_D$  distributions for the plans. Evaluation of these plans provided a test of these metrics in a clinically realistic distribution of doses and LETs.

As specific survival data is not available for the tissues in these treatment plans, RBEs were calculated using a previously published phenomenological model (McNamara *et al* 2015). This model includes tissue  $\alpha/\beta$  ratios and four empirical model parameters which were fit to published experimental data. RBE-weighted doses were then calculated for each plan, with  $\alpha/\beta$  values set to 10 Gy for the medulloblastoma, 1.5 Gy for the prostate. Normal tissue responses were modelled using an  $\alpha/\beta$  of 3 Gy, as typically used when calculating risk of late effects. RBE-weighted doses were then compared to each of the three response metrics for all voxels seeing at least 1% of the prescription dose.

### Sensitivity analysis

A single value of  $\kappa$  was used throughout this work for all endpoints and cell types. This value was obtained by carrying out least-squares fitting to the experimental survival data in both cell lines as presented in figures 2(c) and (f). In addition, only a single value of  $\alpha/\beta$  was assumed for all normal tissue, to simplify the analysis of the correlation between LET- and RBE-weighted doses.

To evaluate the sensitivity of the LET-weighted doses to  $\kappa$  and  $\alpha/\beta$  ratio, we re-calculated the RBE-weighted doses for the two treatment plans for normal tissue  $\alpha/\beta$  ratios ranging from 2 to 10 Gy, corresponding to tissues with very fraction-size sensitive late effects to early responding, fraction-size insensitive tissues. For each  $\alpha/\beta$  ratio, we then calculated the average biological variability across the plans for  $\kappa$  ranging from 0 to 0.15. The resulting average variability, and total range, was then calculated as a function of  $\kappa$ .

## Results

### Cell survival

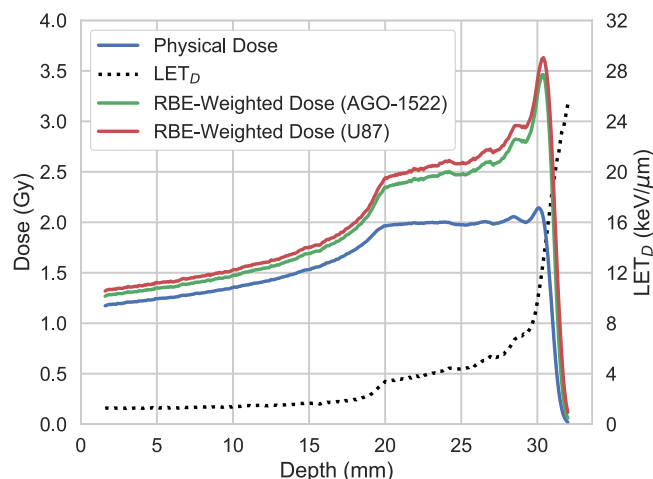
Experimental cell survival values are plotted against each of the response metrics in figure 2 for AGO-1522 and U87 cells. Plotting against dose alone ((a) and (d)) shows the well-established LET-dependence of proton RBE, with an average fit over-estimating cell killing at low LET and under-estimating cell killing at high LET. This leads to a wide biological variability at all doses.

When considering  $D \times \text{LET}_D$  ((b) and (e)), this trend is reversed, with the average fit under-estimating killing at low LET, and over-estimating at high LET, with a greater biological variability than seen for dose alone. This highlights that  $D \times \text{LET}_D$  alone is not a useful metric of biological response, but the trend is in line with suggestions that it is a proxy for additional biological effect, indicating that a combined metric may be useful.

This combined LET-weighted dose,  $D \times (1 + \kappa \text{LET}_D)$ , is plotted in the lower panels ((c) and (f)), with a fitted  $\kappa = 0.055 \pm 0.003 \mu\text{m keV}^{-1}$ , showing significantly improved correlation.  $R^2$  values were 0.84 and 0.88 for AGO-1522 and U87 cells when fit using dose alone, increasing to 0.99 and 0.95 when fit using LET-weighted dose ( $p < 0.05$ , two-tailed Z-test of Fisher-transformed  $R$  values). Thus, applying LET-weighting with a single  $\kappa$  parameter accounts for 60 to 90% of the LET-related variability in survival in these cells. Notably, the use of this single parameter can be seen to be effective despite the different overall radiosensitivities and x-ray  $\alpha/\beta$  ratios of these cell lines (12 Gy and 2.5 Gy), which necessitated the use of considerably different  $\lambda$  parameters in the original analysis. This highlights that by not trying to explicitly predict the magnitude of RBE, LET-weighting can more easily identify exposures with the same biological effect using only a single fitting parameter.

### Spread out Bragg peak RBE

Figure 3 presents dose and  $\text{LET}_D$  distributions across a 2 Gy SOBP delivered using 62 MeV protons with a 10 mm range modulation, together with RBE-weighted doses for AGO-1522 and U87 cells using the published empirical model based on data in figure 2.



**Figure 3.** Dose and  $LET_D$  across 62 MeV SOBp with 10 mm modulation, along with RBE-weighted doses for two cell lines based on empirical fitting to data in figure 2.

For each position along the depth-dose curve, RBE-weighted doses were compared to the different dose metrics, shown in figure 4. Comparing dose alone to RBE-weighted dose shows similar trends to survival, under-estimating the effects of high LET exposures ((a) and (d)). In these plots, trends across the SOBp can be observed—initially, there is good correlation with dose in the low-LET entrance region (dark points) where RBE variations are small. But within the SOBp, dose is roughly constant while LET and RBE increase steeply. And then in the distal tail, dose falls steeply while RBE continues to increase, giving rise to a wide spread in possible biological effects at a given dose.

A similar variability is seen comparing with  $D \times LET_D$ , although once again the trends with LET are reversed ((b) and (e)). An initially rapid rise is seen as dose increases, but within the SOBp the slope is much shallower, as the dependence of RBE-weighted dose on LET is much less than its dependence on physical dose. This also leads to a large over-estimation of effect in the distal tail.

Applying the LET-weighted dose, again using  $\kappa = 0.055 \mu\text{m keV}^{-1}$ , substantially reduces this variability ((c) and (f)) as both physical dose and LET are appropriately taken into account. Improvements are seen in correlation in both cell lines despite the use of a single fitting parameter, with overall performance slightly better in AGO-1522 than in U87 cells. It is important to note that these plots show some curvature rather than the direct proportionality which would be expected of a ‘true’ RBE model, as LET-weighting deliberately does not seek to take into account differences in the underlying tissue biology and  $\alpha/\beta$  ratio. However, by providing a monotonic correlation with biological effect, it can effectively identify regions of high cell killing for use in treatment design or optimisation.

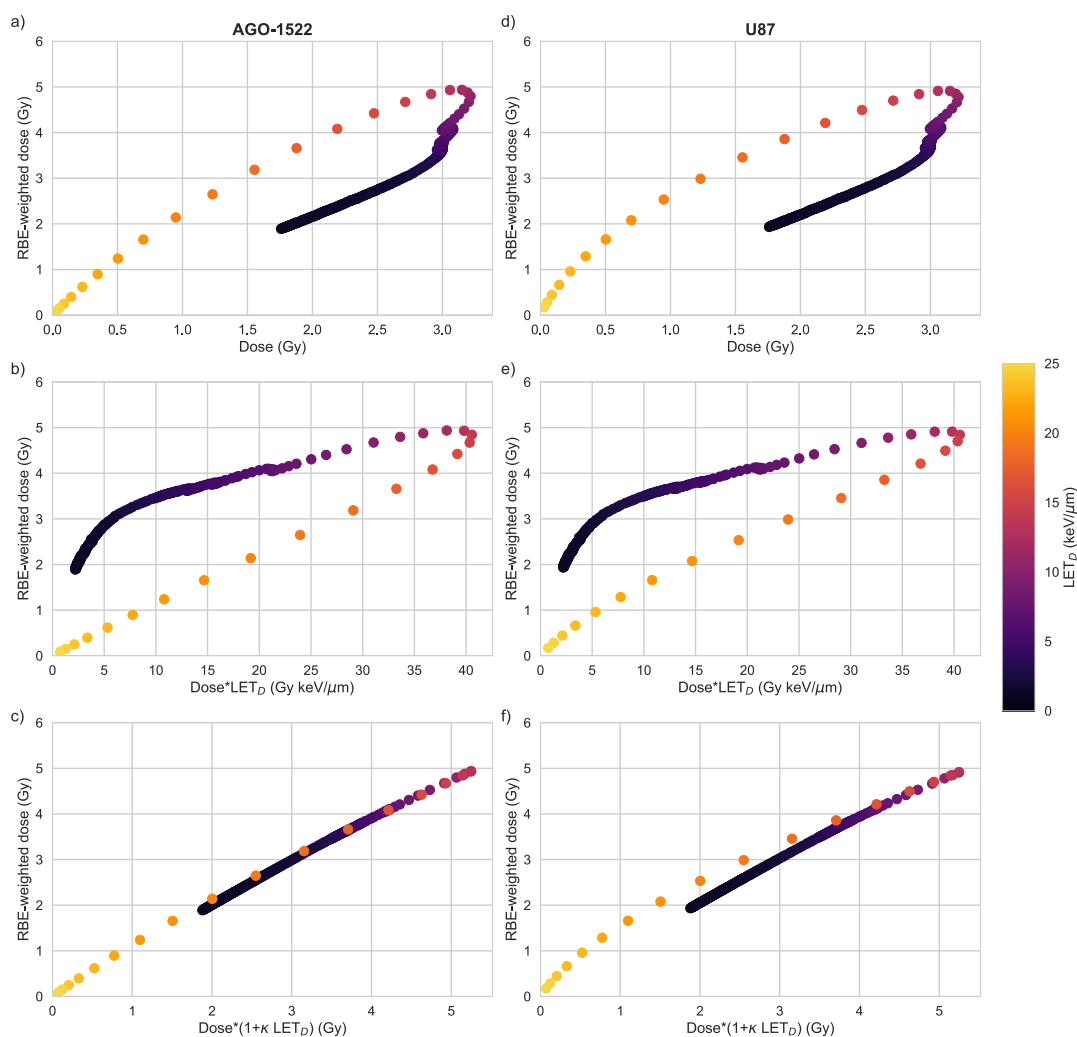
### Clinical treatment plans

Finally, these metrics have been studied in medulloblastoma and prostate clinical treatment plans, with dose and  $LET_D$  distributions shown in figure 5. In common with most proton treatment plans, these approaches have relatively low LETs in the entrance region and much of the target volume, but higher LETs at the end-of-range and at edges of treatment fields. For each voxel in the treatment plan, an RBE-weighted dose has been calculated using the model of McNamara *et al* (2015) and compared against each of the three response metrics, plotted in figure 6.

Comparing dose alone ((a) and (d)) to RBE-weighted dose illustrates the range of biological variability in these plans if they are optimised on physical dose as is currently the case. There is considerable variation in biological effect across the whole dose range, equivalent to over  $\pm 5\%$  of the prescription dose in both sites. This is again due to the lack of incorporation of RBE variability, with higher LET regions seeing increased biological effects.  $D \times LET_D$  ((b) and (e)) is ineffective at resolving this issue, over-estimating the impact of LET and introducing different biological uncertainties.

However, the LET-weighted dose metric ((c) and (f)) greatly reduces this biological variability. By applying the same  $\kappa = 0.055 \mu\text{m keV}^{-1}$  as in the experimental dataset, the biological uncertainty in each plan is reduced to less than 1% across the whole dose range. This suggests that—despite taking a much simpler approach and fitting to only two reference cell lines—this approach effectively reproduces the trends seen in a significantly more complex RBE model fit to a comprehensive dataset.





**Figure 4.** Correlation between RBE-weighted dose and response metrics across a SOBP in AGO-1522 and U87 cells. Each point represents a 0.1 mm slice of the SOBP, coloured according to LET. For dose alone (top (a, d)), there is a large biological uncertainty due to variations in LET, under-estimating effects in high LET regions. As in cell survival, this trend is reversed when considering  $D \times \text{LET}_D$  (middle (b, e)), but the total biological variability is comparable. However, the LET weighted-dose metric (bottom (c, f)) greatly reduces this variability in both cell lines.

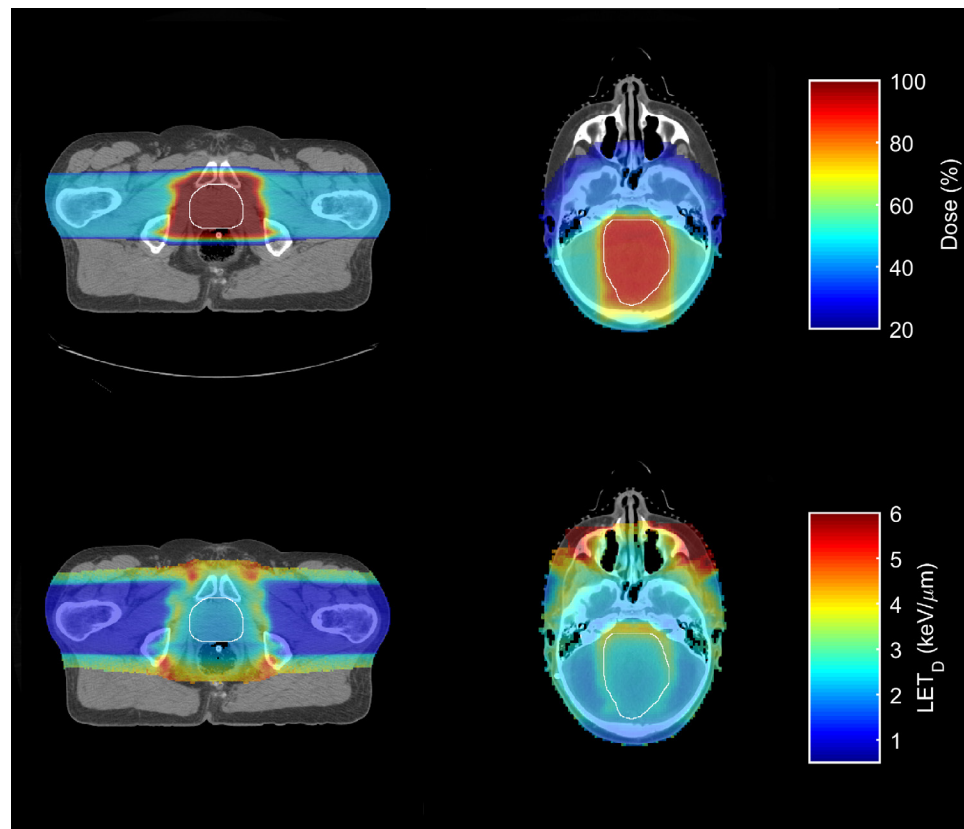
### Sensitivity analysis

A single value of  $\kappa = 0.055 \mu\text{m keV}^{-1}$  has been used throughout this work, determined by minimising the biological uncertainties in an initial *in vitro* experimental dataset. To evaluate the applicability of this assumption, for each treatment plan the average biological uncertainty across the whole plan was calculated for different values of  $\kappa$  and  $\alpha/\beta$ , with the results illustrated in figure 7.

In the limit of  $\kappa = 0$ , this gives the biological variability when using dose alone, which as noted is approximately  $\pm 5\%$  for a normal tissue  $\alpha/\beta$  of 3 Gy as shown in figure 6. This decreases as  $\kappa$  increases, reaching a minimum of less than 1% around  $\kappa = 0.055 \mu\text{m keV}^{-1}$ . This minimum is relatively shallow, with  $\kappa$  values from 0.04 to 0.08 all yielding average biological variabilities of less than 1.5%, suggesting that this metric still offers substantial improvements in predictive power even if the  $\kappa$  value is not precisely optimised.

As the modelled RBE incorporates a dependence on  $\alpha/\beta$ , so too does the magnitude of the biological variability. A shaded range in figure 7(a) shows the range of biological variation for  $\alpha/\beta$  ratios from 2 to 10 Gy for each  $\kappa$ . This shows that both the maximum and minimum variability both initially fall with increasing  $\kappa$ , with the worst-case error minimised around  $\kappa = 0.055 \mu\text{m keV}^{-1}$ .

The  $\alpha/\beta$  dependence is further illustrated in figure 7(b), which shows the average biological variability as a function of  $\alpha/\beta$ , for either physical dose alone or LET-weighted dose with  $\kappa = 0.055 \mu\text{m keV}^{-1}$ . For high  $\alpha/\beta$ , corresponding to early-responding tissues and most tumours, both the total magnitude of the biological variability and the reduction obtained through LET-weighting are relatively small, due to the correspondingly small RBEs. For low  $\alpha/\beta$  tissues, typically late-responding normal tissues with greater fraction sensitivity, LET-weighting is much more effective, with 70%–90% reductions in biological variability for tissues with  $\alpha/\beta$  between 2



**Figure 5.** Dose (top) and  $LET_D$  (bottom) distributions for prostate (left) and medulloblastoma (right) treatment plans. Tumour treatment volumes are outlined in white, while remaining volume is treated as uniform ‘normal tissue’ in this analysis. Each plan delivers a range of doses and LETs using different beam geometries, and have been analysed to explore variations in RBE-weighted dose with other metrics in realistic dose and LET distributions.

and 7 Gy (corresponding correlation plots in the style of figure 6 are presented in the supplementary information ([stacks.iop.org/PMB/63/225009/mmedia](https://stacks.iop.org/PMB/63/225009/mmedia))). In absolute terms, the reduction in biological variability offered by LET-weighting increases monotonically as the  $\alpha/\beta$  ratio falls. However, for very low  $\alpha/\beta$  ratios corresponding to late-responding normal tissues and some tumours (e.g. prostate), the residual variability begins to increase as the initial variability rises more rapidly due to increasing RBE effects.

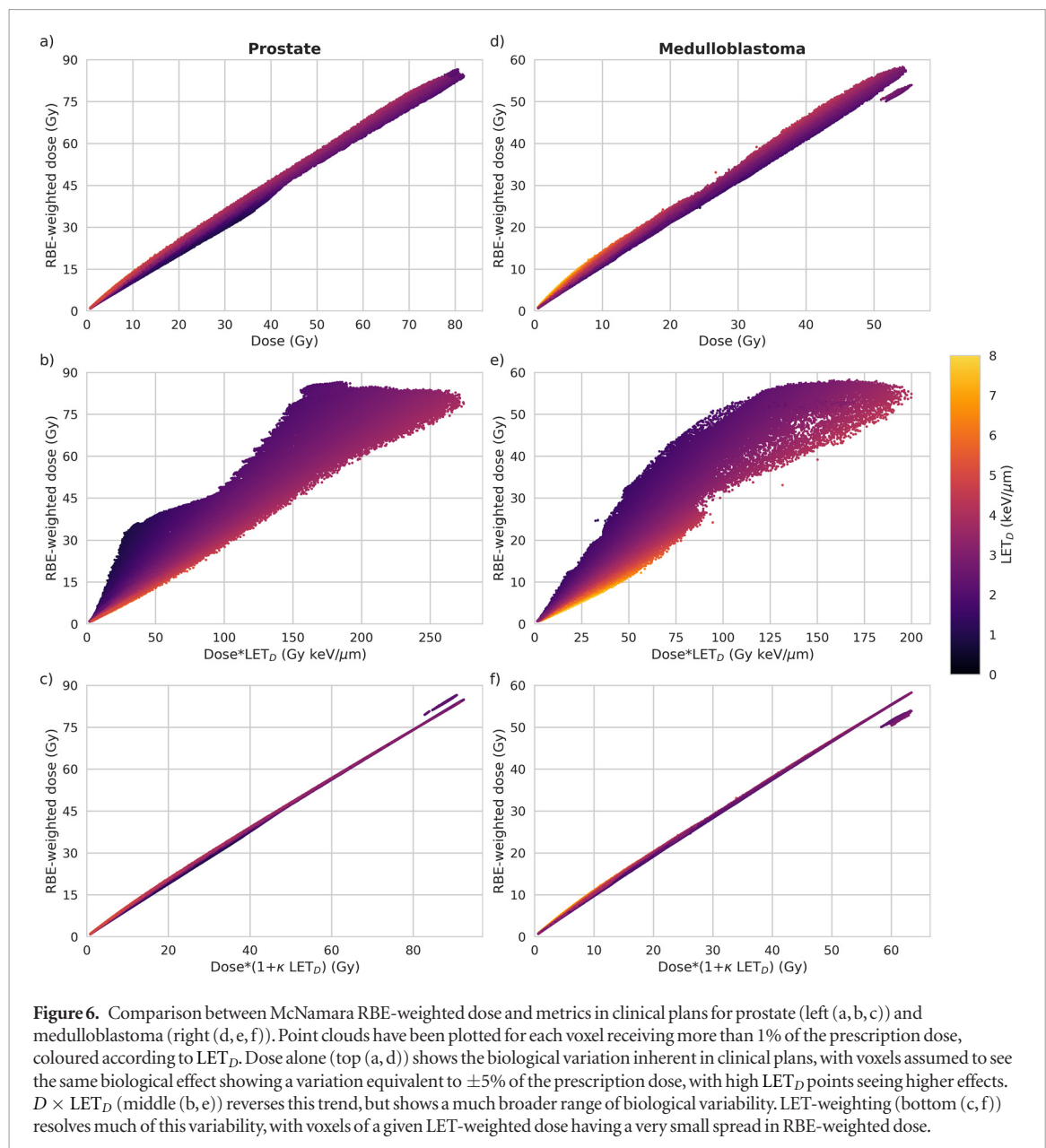
While it is possible to offset this  $\alpha/\beta$  dependence by specifically tuning  $\kappa$  for each  $\alpha/\beta$  value, the magnitude of the improvement is relatively small (an average of 0.6%) and introduces parameters with significant additional uncertainty into the analysis.

## Discussion

Fully optimising treatment plans remains a significant challenge in radiotherapy, particularly in proton therapy where the LET-dependence of biological response adds extra potential dimensions of optimisation (Underwood and Paganetti 2016). However, despite extensive evidence that proton RBE is variable, as seen in reviews of both preclinical datasets (Paganetti 2014) and published RBE models (Rørvik *et al* 2018), most clinical approaches adopt the conservative approach of a constant RBE of 1.1 (Mohan *et al* 2017).

In this work, we explored the use of simplified metrics to reduce the biological variability in radiation response resulting from LET. In particular, we sought to identify metrics which were monotonically related to survival, without the need to explicitly calculate RBE values. By not attempting to generate equivalent photon doses, many aspects of the underlying biology which are subject to large uncertainties (such as underlying tissue radiosensitivity and  $\alpha/\beta$  parameters) can be neglected, greatly simplifying this calculation. The dose-LET product alone was found to not be a suitable approach, as it significantly over-estimates the impact of LET on cell killing and is not suitable for clinical application (as noted elsewhere (Jones 2017)). However, despite its relative simplicity, we find that an LET-weighted dose substantially reduces variability in corresponding RBE-weighted doses predicted by a published RBE model (McNamara *et al* 2015) compared to dose alone. Similarly good performance is seen when LET-weighted doses are compared with other published models (supplementary information).

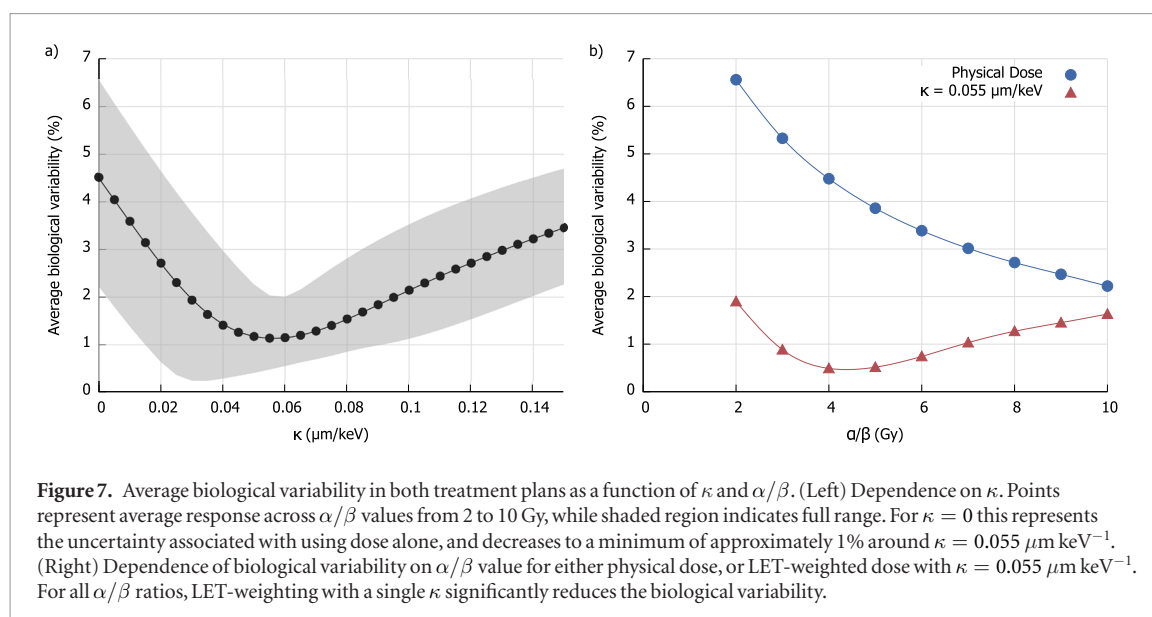
This good performance across various RBE models is perhaps not surprising. Published LET-RBE models are highly correlated, typically agreeing on which regions see higher or lower RBEs even if they disagree on the exact



magnitude of this effect. This points to common underlying assumptions about the relationship between RBE on LET, much of which is effectively captured by this LET-weighted dose approach. Indeed, it is likely that the true underlying behaviour of cellular radiosensitivity actually depends on more complex variations in cellular energy deposition on the sub-cellular scale, which is necessarily only approximated by factors like LET (Hawkins 2003, Scholz and Elsässer 2007, McMahon *et al* 2017). As a result, it may be useful to also explore if other biophysical parameters which can be more directly measured, such as the dose-mean lineal energy ( $\overline{y_D}$ ), may also provide useful correlations with biological effect (Tran *et al* 2017).

These approaches have the potential to support planning in proton therapy. A major ongoing area of research is in optimising therapy to account for elevated end-of-range LETs in normal tissue which may lead to increased complication rates (Buchsbaum *et al* 2014). This metric can help guide such studies by identifying regions, which would be expected to show the greatest deviation from physical dose alone. In addition, while optimising dose and LET independently may go some way to addressing RBE effects (Bassler *et al* 2010, Unkelbach *et al* 2016, Wan Chan Tseung *et al* 2016), because of the interplay between these parameters it is possible that reduction in physical dose will be offset by increases in LET, or vice versa. By providing a metric which is monotonic in biological effect, optimisation of LET-weighted doses has the potential to offer more biologically robust solutions (Mohan *et al* 2017).

It is important to note that this approach is not a true RBE model, and systematic differences between LET-weighted dose and RBE-weighted dose can be seen (figures 4 and 6). For example, around 60 Gy in each treatment plan there is a systematic deviation on the order of 5% between LET-weighted and RBE-weighted dose. This increases at higher doses as the relationship between the two quantities is not perfectly linear. This effect



arises because this approach does not attempt to take into account curvature of dose response and tissue-specific  $\alpha/\beta$  values. This leads to differences in the curvature and scaling of the LET-weighted dose versus RBE-weighted dose relationship, with high  $\alpha/\beta$  tissues seeing shallower, straighter curves compared to low  $\alpha/\beta$  tissues. This can be seen in figure 6, where separate small clusters of points are seen at high doses, corresponding to tumour volumes with different  $\alpha/\beta$  ratios to the normal tissue. This effect is also influenced by the dependence of RBE on the  $\alpha/\beta$  of a given tissue, with high  $\alpha/\beta$  tissues such as medulloblastoma being expected to see an RBE close to 1, while low  $\alpha/\beta$  tissues such as prostate and late responding normal tissues would be expected to see much larger RBEs, meaning any RBE model must be applied with care. Further investigations which explore full RBE-weighted dose-volume effects in each target tissue with their individual radiosensitivity parameters will be necessary to confirm the wider applicability of this approach.

As a result of these factors, this approach cannot be used to set the targets for optimisation such as delivered dose or dose-volume relationships, which will continue to have to be guided by clinical experience and data as at present. However, once these targets have been established, correlations between biological effect and LET-weighted dose remain good for any given tissue, enabling it to serve as a robust tool in planning optimisation even in the light of uncertainties in parameters such as the  $\alpha/\beta$  ratio. As the exact shape of the relationship between biological effect and LET-weighted dose may remain uncertain for a particular cancer, it may also be advantageous to apply parameter-independent plan comparison techniques when comparing different plans generated by this approach (Stavreva *et al* 2010).

Finally, in this work, a value of  $\kappa = 0.055 \mu\text{m keV}^{-1}$  has been used based on a limited sample of *in vitro* experimental data. This is necessarily an approximation to the true underlying biology, and as shown in figure 7 leads to different degrees of residual biological variability in systems with different  $\alpha/\beta$  values, which may require caution if this model is to be applied to tissues such as CNS which may have particularly low  $\alpha/\beta$  values at the limits of this approach's tested range. While in principle  $\kappa$  could be further refined to better approximate the underlying biology by introducing corrections for tissue  $\alpha/\beta$  ratios or the dose and  $\text{LET}_D$  characteristics of the treatment plan, as shown in figure 6 and the supplementary information this relatively simple approach performs well compared to more sophisticated RBE models. This suggests that the benefits from the introduction of more complex variations of this metric would be relatively marginal.

Before this approach can be translated into clinical practice, more comprehensive planning and analysis studies are needed to fully assess the performance of this model across the full range of clinical scenarios where it may be applied, quantifying the residual uncertainty when LET-weighted dose is used. As an initial assessment, optimisation studies can be carried out comparing treatments optimised using LET-weighted dose to those generated using RBE models, to determine how effectively this simpler approach reproduces the full complexity of RBE models. In addition, if suitable data is available this approach can be used retrospectively to identify potential biological effect 'hot-spots' in clinical treatment plans, to determine if these correlate with observed toxicities. Such studies should include a detailed analyses which fully incorporates all features of the clinical problem for different sites (such as varying  $\alpha/\beta$  ratios and normal tissue sensitivity for consequential late effects as seen in the CNS), and it is important to bear in mind that all RBE models considered here are based on cell survival endpoints which may not correspond directly to the RBE seen for dose-limiting late normal tissue toxicities. As a result, full validation of any RBE models is likely to require extensive, well-controlled clinical trials designed to provide greatest sensitivity to variations in treatment LET.

## Conclusions

It has been shown that an LET-weighted dose metric,  $D \times (1 + \kappa \text{LET}_D)$ , reduces biological variability resulting from changing RBE in proton therapy almost as effectively as full RBE models. While this cannot be used to set absolute dose constraints in general, it effectively identifies regions which may see elevated biological effects due to high LET, and may prove a valuable tool for therapy optimisation and retrospective response analysis without the need for the added complexity of full RBE models.

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## Conflict of interest

None.

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